Impact of Long-Term Naltrexone Treatment on Growth Hormone and Insulin Secretion in Hyperandrogenic and Normal Obese Patients

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The growth hormone (GH) response to stimulation tests is impaired in obesity. Moreover, obese patients exhibit a "paradoxical" increase of GH to GH-releasing hormone (GHRH) stimulation after food ingestion; this paradoxical response is reversed by naloxone infusion. On the other hand, β-endorphin seems to exert profound effects on insulin release. Recent studies also demonstrated an impairment of GH response to several stimuli in polycystic ovary syndrome (PCOS), a condition associated with obesity, hyperinsulinism, and insulin resistance. Chronic inhibition of opioid tone by the opioid antagonist naltrexone (NTX) is able to reduce the insulin response to an oral glucose tolerance test (OGTT) in hyperinsulinemic PCOS patients. Since insulin and GH may reciprocally influence their secretion and the opioid system may have a role in the pathogenesis of hyperinsulinemia and reduced GH secretion, we have explored the involvement of these neuroendocrine mechanisms in essential obesity and in obesity associated with hyperandrogenism by a long-term treatment with an opiate antagonist. We tested seven obese patients affected by PCOS, seven matched women with essential obesity (EO), and five non-obese control subjects. All patients, in the follicular phase, underwent an OGTT (75 g) and basal hormone assay. Two days later, patients were subjected to a GHRH test. The patients then had 4 weeks of treatment with NTX 50 mg/d. Following continuation of the treatment, OGTT and GHRH tests were repeated. Insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) plasma concentrations were also determined in the basal condition before and after NTX treatment. NTX treatment reduced fasting insulin levels in patients with EO ($P < .05$) and restored a normal GH response to GHRH without affecting IGF-1 and IGFBP-3 levels. In PCOS subjects, NTX reduced the insulin response to a glucose load and failed to modify the blunted GH response to GHRH. Our data suggest a significant difference in opioid system function in PCOS and EO subjects, indicating a particular form of obesity in PCOS. The opiate antagonist treatment in EO may act through the reduction of negative insulin feedback on GH secretion. In PCOS patients, the failure to improve GH secretion in obese hyperandrogenized patients may be related to a high opioidergic tone or to the inhibitory predominance of other neurotransmitters.

IT IS WELL KNOWN that impairment of the growth hormone (GH) response to a variety of stimulatory tests, including direct stimulation with GH-releasing hormone (GHRH), is present in obesity.[1] In fact, a partial restoration of GH responsiveness after weight loss has been observed.[2] Moreover, obese patients exhibited a "paradoxical" increase of GH to GHRH in relation to food ingestion as compared with controls, in whom there was an inhibitory effect on GH response[3]; this paradoxical response was reversed by naloxone infusion, suggesting that the opioid tone could in part account for the alteration of GH secretion.[4] Moreover, opioid peptides are involved in a complex way in the control of appetite and in the pathogenesis of obesity: β-endorphin plasma levels are increased in obese subjects,[5] and this increase is not corrected by weight loss[6]; pancreatic β cells show an increased sensitivity to β-endorphin[7]; and β-endorphin is increased in the pituitary of genetically obese rats.[8]

Polycystic ovary syndrome (PCOS) is a clinical condition characterized by reproductive disorders, hyperandrogenism and a variety of metabolic effects such as obesity, hyperinsulinism, and insulin resistance.[9-11] Recent studies have also demonstrated an impairment of GH response to several stimuli in PCOS.[12,13] This effect is only partially due to obesity, since lean hyperinsulinemic subjects showed a similar blunted enhancement of GH after GHRH injection.[12] Moreover, the demonstration of β-endorphin in human endocrine pancreas[14] and the finding of elevated plasma immunoreactive β-endorphin in PCOS patients compared with control subjects[15] suggest a possible involvement of endogenous opiates in glycoregulation. In previous studies, we demonstrated that chronic inhibition of opioid tone by the opioid antagonist naltrexone (NTX) was able to reduce the insulin response to an oral glucose tolerance test (OGTT) in hyperinsulinemic PCOS patients without affecting glycemic levels.[16]

Overall, these data suggest that hyperinsulinemia, obesity, and opioid tone could be related to each other. In particular, they can influence in a complex manner the function of the GH/insulin-like growth factor-I (IGF-I) axis. In PCOS, hyperandrogenism is present, and thus it is possible that differences in endocrine-metabolic features in this syndrome may be partially attributed to the steroid milieu.

Since insulin and GH may reciprocally influence the secretion of one another and the opioid system may have a role in the pathogenesis of hyperinsulinemia and reduced GH secretion, we have explored the involvement of these neuroendocrine mechanisms in essential obesity (EO) and in obesity associated with hyperandrogenism by a long-term treatment with an opiate antagonist.

SUBJECTS AND METHODS

Patients and Study Protocol

The present study included seven obese patients with PCOS, seven matched women with EO, and five non-obese control subjects. PCOS patients and non-obese controls were attending the Department of Obstetrics and Gynecology of our University because of chronic anovulation (PCOS) or sterility due to tubal disease (controls). Women with EO attended the Institute of Endocrinology. Informed consent was

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obtained from each patient. The study was approved by the Institutional Board of the Department of Obstetrics and Gynecology.

All women were in good health and euthyroid and had a normal glomerular filtration rate (as demonstrated by normal creatinine clearance levels). None of them had taken any medication known to affect carbohydrate metabolism or gonadal function for at least 3 months before the study. All PCOS patients had spontaneous onset of puberty and normal sexual development. Adrenal enzymatic defects were excluded by a corticotropin test according to the criteria of New et al.[17]

PCOS was diagnosed by clinical findings (presence of amenorrhea or oligomenorrhea and hirsutism), hormonal characteristics (elevated plasma androgen concentration), and bilaterally normal or enlarged ovaries with at least seven to 10 microcysts (<5 mm in diameter) at the time of transvaginal ultrasound examination. PCOS diagnoses were confirmed at laparoscopy. A normal luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio was not considered an exclusion criterion. One PCOS patient showed evidence of acanthosis nigricans.

The waist to hip ratio (WHR) was calculated from circumferences measured in the supine position. EO was defined when the body mass index (BMI) exceeded 30 kg/m^2 [18] in the absence of other endocrinopathies. For the purpose of the study, only patients (both PCOS and EO) with a BMI greater than 30 were recruited. All patients with EO and normal-weight controls had regular menstrual cycles. None of these patients had hirsutism or acanthosis nigricans.

All studies were performed in the follicular phase, on cycle days 6 to 7 after spontaneous or progestin-induced menses. The patients were hospitalized. After following a standard carbohydrate diet (300 g/d) for 3 days and fasting overnight for 10 to 12 hours, they underwent an OGTT (75 g) and basal hormone assay. Blood samples were collected at −30, 0 (basal), 60, 90, and 120 minutes from the glucose load.

Two days later, patients were subjected to a GHRH test. At 7 AM, GHRH (Geref; Serono, Milan, Italy) was injected intravenously at a dose of 1 μg/kg body weight. Blood samples were collected at −30, 0 (basal), 15, 30, 60, and 90 minutes from peptide administration for the determination of GH plasma concentrations.

The patients then left the hospital and had 4 to 5 weeks of treatment with 50 mg/d NTX, an oral narcotic antagonist (Antaxone; Vicenza, Italy), taken in the evening. In the absence of spontaneous menstrual bleeding, a progestin test was performed after 3 weeks of NTX treatment. Following continuation of NTX treatment, OGTT and GHRH tests were repeated in randomized order in the second period of hospitalization at menstrual days 6 to 7. The two tests were performed on 2 subsequent different days, 12 hours after the last dose of NTX.

Assays

All blood samples were promptly centrifuged. Samples for glucose were assayed immediately, whereas samples for other determinations were stored at −20°C until assayed. Insulin and glucose were assayed in all OGTT samples. Furthermore, LH, FSH, Prolactin, estradiol (E_2), testosterone (T), 17OH-progesterone (17OHP), androstenedione (A), dihydroepiandrosterone sulfate (DHEAS), sex hormone–binding globulin (SHBG), IGF-I, and IGF-binding protein-3 (IGFBP-3) plasma concentrations were also determined in the basal condition before and after NTX treatment.

All hormone concentrations were determined by commercial radioimmunoassay (RIA) kits (Radim, Pomezia, Italy). Glucose concentrations were determined by the glucose oxidase technique.

All hormone levels were measured in duplicate by RIA methods using commercial kits (Radim). The immunoradiometric assay (IRMA) on solid phase (coated-tube), based on the monoclonal double-antibody technique, was used for LH, FSH, and SHBG detection. Steroids were assayed by a RIA direct method in human serum or plasma. Insulin was assayed using an RIA method. Intraassay and interassay coefficients of variation were as follows: LH, 5.6% and 9.1%; FSH, 6.9% and 8.4%; E_2, 2.3% and 3.5%; T and A, 6.1% and 9.3%; insulin, 5.1% and 6.2%; and SHBG, 6.9% and 8.5%.

GH was determined by the IRMA method using commercial kits from Radim. Intraassay and interassay coefficients of variation were, respectively, 2.5% and 5.8%. The lowest amount of GH detected was 0.04 μg/L.

Plasma IGF-I level was measured by the RIA method using kits from Nichols Institute (San Juan Capistrano, CA). Soluble IGF-I was separated from interfering binding proteins by precipitation with ethanol-HCl. IGF-I normal values range from 170 to 330 μg/L (for ages >25 years) and 260 to 540 μg/L (for ages <25 years). Plasma IGFBP-3 level was measured by a RIA method using commercial kits from Mediagnost (Tubingen, Germany), previously described by Blum et al.[19] For molar comparison between IGF-1 and IGFBP-3, we have considered 30.5 kd the molar weight of IGFBP-3, as suggested by Juul et al.[20]

For each determination, all samples from the same patient were assayed simultaneously. Intraassay and interassay coefficients of variation were less than 8% and 15%, respectively.

Data Analysis

An abnormal glycemic response to the OGTT was defined according to the criteria of the National Diabetes Data Group.[21]

All results are expressed as the mean ± SD. Insulin and GH plasma concentrations were also expressed as the area under the curve (AUC) after glucose load or GHRH injection, respectively, and calculated by the trapezoidal rule.

Distribution of the data was tested by Kolmogorov-Smirnov test to verify whether the samples come from a specified distribution, and we found that the data were not normally distributed. The significance of differences between the same tests performed before and after NTX treatment was assessed by the nonparametric Wilcoxon rank-sum test. Comparison between different study groups has been performed with the nonparametric Mann-Whitney *U* test. The level of statistical significance was set at *P* less than .05.

RESULTS

Table 1 shows clinical parameters of the different study groups at the start of the study. Obese PCOS patients showed significant differences for WHR, hirsutism score, and length of menstrual cycle versus patients with EO. Age was similar between the groups, and no difference was seen for BMI among PCOS and EO groups. During treatment, we did not observe any significant change in BMI, WHR, and hirsutism score.

Basal Hormone Levels

Table 2 shows baseline hormone plasma levels before and after NTX treatment. Patients with PCOS had significantly higher plasma LH, A, and T levels compared with EO and

Table 1. Clinical Features of PCOS Obese Patients, Patients With EO, and Non-obese Control Subjects

Feature	PCOS (n = 7)	Obese (n = 7)	Controls (n = 5)
Age (yr)	26.2 ± 5.1	28.5 ± 7.3	30 ± 5.7
BMI (kg/m^2)	35.5 ± 4.6§	34 ± 3.2§	23.6 ± 2
WHR	0.91 ± 0.05*	0.77 ± 0.06	0.75 ± 0.04
Hirsutism score	17.8 ± 2.25†	3.5 ± 0.9	2.5 ± 0.4
Length of cycle (d)	48.8 ± 7.1‡	26.7 ± 2.9	25.2 ± 3.8

*$P < .05$, PCOS *v* obese and controls.
†$P < .01$, PCOS *v* obese and controls.
‡$P < .001$, PCOS *v* obese and controls.
§$P < .001$, PCOS and obese *v* controls.

Table 2. Hormonal Characteristics of PCOS Obese Patients, Patients With EO, and Non-obese Control Subjects Before and After NTX Treatment

Characteristic	PCOS		Obese		Controls	
	Before	After	Before	After	Before	After
LH (IU/L)	13.2 ± 5.5*†	11.7 ± 4.5	7.8 ± 2.6	8.6 ± 3.7	6.81 ± 1.9	5.6 ± 2.3
FSH (IU/L)	5.5 ± 2.1	5.33 ± 1.5	7.7 ± 3.3	7.8 ± 3.8	7.3 ± 3.2	7.5 ± 4.1
E_2 (pmol/L)	167.3 ± 81.7	175.5 ± 95	172.3 ± 97.4	169.9 ± 8	125.7 ± 77.4	139.2 ± 89
T (nmol/L)	2.8 ± 1.1‡§	2.6 ± 0.8	1.7 ± 0.4‖	1.91 ± 0.7	1.04 ± 0.6	1.07 ± 0.6
A (nmol/L)	7.6 ± 1.5§¶	6.4 ± 1.5#	3.6 ± 1.2	3.4 ± 1.5	3.1 ± 1.4	3.02 ± 0.8
DHEAS (μmol/L)	6.43 ± 1.7	5.89 ± 2.8	5.8 ± 3.3	5.7 ± 2.9	4.5 ± 1.7	4.7 ± 2.3
17OHP (nmol/L)	1.8 ± 1.3	1.7 ± 1.1	1.68 ± 0.9	1.55 ± 1.2	1.05 ± 0.5	1.12 ± 0.7
PRL (μg/L)	22.3 ± 15.8	18.9 ± 16	19.1 ± 14	20.1 ± 11.9	14.6 ± 13	13 ± 9.8
SHBG (nmol/L)	18.9 ± 10.9**	16.3 ± 7.9††	22.7 ± 9.8‡‡	22.4 ± 11§§	53.7 ± 17.4	56 ± 22.3
Insulin (μU/mL)	16.5 ± 8.9†	14.6 ± 9.4†	23.9 ± 13.2‖ ‖‖	12.4 ± 5.6¶¶	7.8 ± 3.2	6.1 ± 0.5
IGF-I (μg/L)	166.1 ± 57*	161.9 ± 33#	249 ± 69	290 ± 109	198.7 ± 51	182 ± 39
IGFBP-3 (μg/L)	4,802 ± 1,887	4,434 ± 1,492	3,721 ± 578	3,699 ± 732	3,926 ± 634	3,978 ± 598
IGF/IGFBP-3 (molar ratio)	0.14 ± 0.05†‡	0.14 ± 0.04#	0.27 ± 0.11	0.31 ± 0.10	0.20 ± 0.01	0.18 ± 0.01

*$P < .05$, PCOS *v* obese before NTX.
†$P < .05$, PCOS *v* controls before NTX.
‡$P < .01$, PCOS *v* obese before NTX.
§$P < .001$, PCOS *v* controls before NTX.
‖$P < .05$, obese *v* controls before NTX.
¶$P < .001$, PCOS *v* obese before NTX.
#$P < .01$, PCOS *v* obese after NTX.
**$P < .01$, PCOS *v* controls before NTX.
††$P < .01$, PCOS *v* controls after NTX.
‡‡$P < .01$, obese *v* controls before NTX.
§§$P < .01$, obese *v* controls after NTX.
‖‖$P < .05$, before *v* after NTX.
¶¶$P < .05$, obese *v* controls after NTX.

control groups, whereas SHBG plasma levels were lower as compared with controls.

Fasting insulin levels were significantly higher in both PCOS and EO patients with respect to controls (PCOS *v* controls, $P < .05$; EO *v* controls, $P < .05$; PCOS *v* EO, NS). NTX treatment reduced fasting insulin levels only in patients with EO ($P < .05$).

PCOS subjects had lower baseline GH values versus controls (0.22 ± 0.12 *v* 1.7 ± 1.1 μg/L, $P < .05$). NTX administration did not affect basal plasma GH levels in both PCOS and EO patients, as well as controls.

IGF-I and IGFBP-3 plasma levels were also measured before and after NTX treatment. Basal IGF-I concentrations were significantly lower in PCOS patients versus EO patients ($P < .05$), whereas IGFBP-3 plasma concentrations were similar. Thus, the IGF-I/IGFBP-3 ratio was significantly lower in PCOS versus EO patients ($P < .01$) and controls ($P < .05$).

The treatment did not determine any significant change in IGF-I or IGFBP-3 levels in all groups.

Insulin Response to OGTT

Figure 1 shows the insulin response to the OGTT in the different study groups before and after NTX treatment. The AUC and peak values for insulin after glucose ingestion were significantly higher in PCOS patients than in EO patients and even higher in control subjects. NTX treatment significantly reduced both parameters in PCOS, but failed to modify the insulin response to the glucose load in EO patients and controls. After treatment, the difference for AUC and peak insulin levels

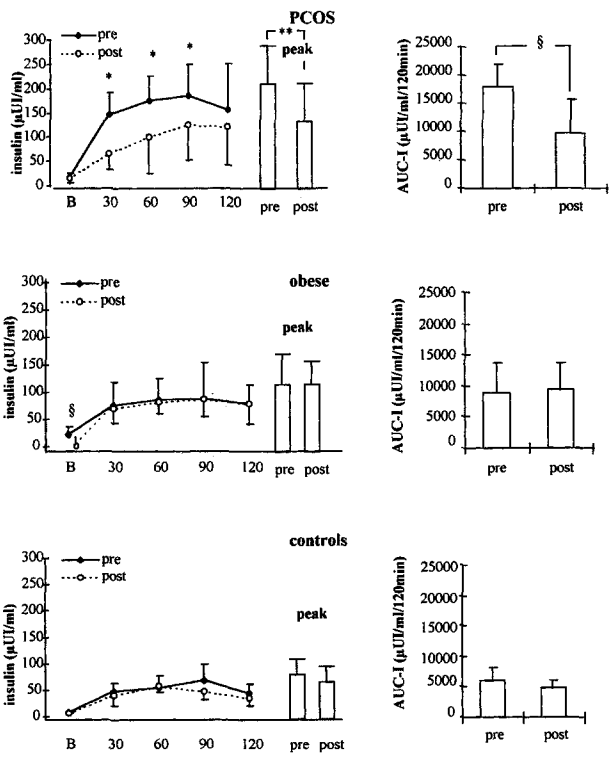

Fig 1. Insulin response to OGTT in the different study groups before and after NTX treatment. (Left) Insulin plasma level and insulin peak after glucose load; (Right) AUC of insulin (AUC-I) after glucose load. *$P < .05$; **$P < .01$; §$P < .02$.

among PCOS and EO groups was abolished. No patients exhibited impairment of glucose tolerance before and after NTX administration.

GH Response to GHRH Injection

Figure 2 shows the GH response to GHRH injection in the different study groups. Before the opioid antagonist treatment, AUC-GH and GH peak values were similar in PCOS and EO patients. Both parameters were significantly lower than in controls.

After NTX, both AUC-GH and GH peak values were significantly increased in EO patients, whereas no significant change in PCOS subjects was found. Conversely, NTX treatment significantly reduced AUC-GH and GH peak levels in controls.

DISCUSSION

Several clinical and endocrine features differentiated PCOS obese subjects from patients with EO. PCOS obese patients showed clinical signs of androgen excess and higher circulating androgen levels and exhibited a significantly higher WHR with respect to patients with EO. In recent reports, a significant positive correlation between peripheral blood androgen concentration and WHR was reported.[22] Moreover, in several studies, a positive relationship between circulating androgen levels and hyperinsulinemia was found.[23] Insulin synergizes the gonadotropin action on the theca compartment, suggesting an important role of this hormone in the pathogenesis and maintenance of the syndrome through a paracrine mechanism. However, hyperinsulinemia and insulin resistance are heterogenously represented in the general PCOS population. These endocrine-metabolic features are present in a large number of obese subjects and also in 30% to 40% of lean subjects.[24]

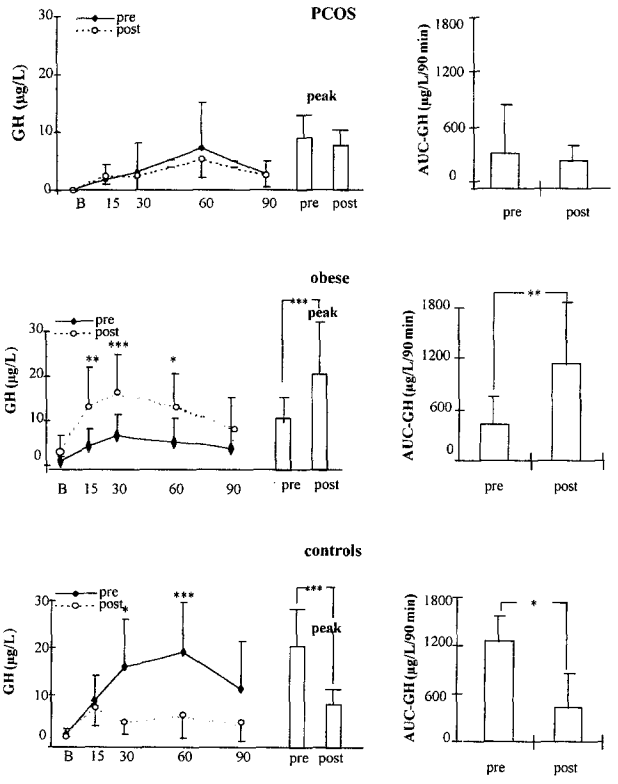

Fig 2. GH response to GHRH injection in the different study groups before and after NTX treatment. (Left) GH plasma level and GH peak after GHRH injection; (Right) AUC-GH after GHRH injection. *$P < .05$; **$P < .01$; ***$P < .02$.

Several lines of evidence suggested that opioids are involved in the pathogenesis of obesity and in the modulation of appetite.[25] Furthermore, in PCOS patients, the finding of elevated plasma immunoreactive β-endorphin compared with control levels and the linkage between opiates and insulinemic pattern suggest a possible involvement of endogenous opiates in glucoregulation.[16]

In agreement with our previous data, the present study shows that treatment with the opiate receptor blocker NTX is able to significantly reduce the insulin AUC after OGTT in PCOS but not in EO patients. In a recent study, we hypothesized that chronic inhibition of opioid tone reduces hyperinsulinemia, influencing hepatic insulin extraction more than pancreatic secretion.[26] Furthermore, we described a significant negative correlation between the insulin incremental area and insulin hepatic extraction, but not with BMI, suggesting an augmented insulin metabolic clearance in hyperinsulinemic compared with normoinsulinemic PCOS patients.

In patients with EO, NTX treatment significantly reduced fasting insulin levels ($P < .05$) even if the secretory response to the OGTT was not affected. These data suggest that in EO, basal insulin secretion may be modulated by the opioid system; conversely, according to Vettor et al,[27] the response to the oral glucose load seems to be independent of opioid modulation.

On the other hand, obesity is associated with an impaired GH response to direct stimuli such as GHRH alone,[3] GHRH plus pyridostigmine, and GHRH plus arginine.[28] The opioid system seems to contribute to the complex modulation of GH secretion in obese subjects. In a previous study, De Marinis et al[4] demonstrated that obese subjects showed a paradoxical increased postprandial response to GHRH, which is reversed by naloxone infusion. Since it is known that the opioid system stimulates GH release,[29,30] it was hypothesized that food ingestion could increase the endogenous opioid tone and consequently GH secretion, either by induction of GHRH activity or by blockade of the somatostatin inhibitory effect.

However, Lanzone et al[12] demonstrated that the GH response to GHRH is blunted in PCOS patients with respect to corresponding weight-matched controls. Among such patients, obese and hyperinsulinemic subjects exhibited a markedly decreased response of GH to GHRH, thus suggesting that factors other than obesity account for this endocrine imbalance in PCOS.

In our study, patients with EO showed, after long-term NTX treatment, a significant increase in GH response, confirming the relevant role of the opioid system in the regulation of GH secretion in these patients. This response is opposite to that observed in normal-weight controls, in whom GHRH-induced GH release is blunted during NTX. This response is in agreement with our previous studies showing an inhibition of the GH response during acute blockade of opioid receptors by naloxone.[31]

The difference between controls and patients with EO could be ascribed to hyperinsulinism observed in obese patients. In

vitro studies showed that insulin is able to reduce GH release from rat pituitary,[32] and we hypothesized that hyperinsulinemia, frequently associated with obesity, could be related to impaired GH secretion. Our data indicate a role of hyperinsulinemia in the modulation of opioid action on GH secretion in patients with EO. In fact, after long-term NTX treatment, we observed a significant reduction in basal insulin secretion and a significant increase in the GH response to GHRH both as peak values and AUC. Moreover, PCOS patients showed higher insulin AUC and lower AUC-GH levels compared with patients with EO, in whom no differences after NTX treatment were found in the GH response to GHRH. Since both obese study groups had a similar BMI, our data strengthen the contention that the excess body weight could not entirely account for these different endocrine pictures.

To explain these differences between NTX effects in EO and PCOS patients, different hypotheses can be formulated:

(1) Despite NTX inhibition of insulin-stimulated release in PCOS, fasting insulin levels remain too high to allow an enhancement of GH secretion. Alternatively, a greater GH sensitivity to the negative feedback action of insulin could be present in these patients.

(2) Another mechanism may be ascribed to IGF-I and related binding proteins. Recent data indicate that circulating and exogenously infused IGF-I suppresses GH release in humans, probably via mechanisms in the hypothalamus and/or pituitary gland.[33] Despite low GH levels, elevated IGF-I concentrations have been reported in obesity,[34] and it has been demonstrated that a massive weight loss can restore the 24-hour GH release profile, IGF-I levels, and IGF/IGFBP-3 molar ratio in obese subjects[35,36]; thus, IGF-I was suggested as a possible mediator of the impaired GH secretion.[36] This hypothesis does not completely explain the differences between PCOS and EO, since IGF-I and IGF/IGFBP-3 levels were lower in PCOS versus EO and did not change after NTX. However, the chemical structure of IGF-I and insulin is similar, and it has been recently reported that high plasma insulin levels could activate the IGF-I receptor.[37] It may be hypothesized that elevated insulin binds the IGF-I receptor and induces an inhibitory effect on GH secretion.

(3) It is also possible that the steroid milieu of PCOS may, in part, account for the differences among EO and PCOS groups. Although we have not observed a significant change in androgen levels following NTX treatment, the greater androgen levels in PCOS could modify the sensitivity to NTX itself.

(4) Finally, central neurotransmitters other than peripheral factors (insulin, IGFs, and androgens) could be differently involved in GH secretion in EO and PCOS. Recently, Lee et al[13] observed an improvement in GH response after pyridostigmine and L-DOPA in PCOS. It could be related to a disturbance of central somatostatinergic tone. Morris et al,[38] administering the octreotide peptide, showed that women with PCOS were more sensitive to its effects in decreasing IGF-I and increasing IGFBP-3 than normal controls. This suggests that in PCOS, a different level of sensitivity in the somatotrophic axis and other neurotransmitters such as somatostatin can affect GH secretion. A stronger somatostatinergic tone or an enhanced sensitivity to somatostatin could block GH secretion in PCOS, despite NTX treatment.

The bulk of the data reported here suggest a significant difference in opioid system function in PCOS and EO patients, indicating a particular form of obesity in PCOS. The opiate antagonist treatment in EO is able to reduce basal insulin levels and to augment the GH response to GHRH acting directly or indirectly through the reduction of negative insulin feedback on GH secretion. In PCOS patients, the opioid antagonist–mediated reduction of the insulin response to OGTT seems the only effect of treatment. It is possible that the failure to improve GH secretion in obese hyperandrogenized patients is related to high opioidergic tone or to the inhibitory predominance of other neurotransmitters.

REFERENCES

1. Williams T, Berelowitz M, Joffe S, et al: Impaired growth hormone responses to growth hormone–releasing factor in obesity. N Engl J Med 311:1403-1407, 1984

2. Jung R: Endocrinological aspects of obesity, in James WPT (ed): Clinics in Endocrinology and Metabolism, vol 13: Obesity. Philadelphia, PA, Saunders, 1984 pp 597-612

3. De Marinis L, Folli G, D'Amico C, et al: Differential effects of feeding on the ultradian variation of the growth hormone response to GH-releasing hormone in normal subjects and patients with obesity and anorexia nervosa. J Clin Endocrinol Metab 66:598-604, 1988

4. De Marinis L, Mancini A, Folli G, et al: Naloxone inhibition of postprandial growth hormone releasing hormone–induced growth hormone release in obesity. Neuroendocrinology 50:529-532, 1989

5. Scavo D, Facchinetti F, Barletta C, et al: Plasma beta-endorphin in response to oral glucose tolerance test in obese patients. Horm Metab Res 19:204-207, 1987

6. Pasquali R, Cantobelli S, Casimirri F, et al: The role of the opioid peptides in the development of hyperinsulinemia in obese women with abdominal body fat distribution. Metabolism 41:763-767, 1992

7. Mason JS, Haber D: Endogenous opiates modulate insulin secretion in flushing non–insulin-dependent diabetics. J Clin Endocrinol Metab 54:693-697, 1982

8. Khawaja XZ, Bailey CJ, Green IC: Central mu, delta and kappa opioid binding sites and brain and pituitary β-endorphin and met-enkephalin in genetically obese (ob/ob) and lean mice. Life Sci 44:1097-1105, 1989

9. Goldzieher JW: Polycystic ovarian disease. Fertil Steril 35:371-394, 1981

10. Barbier RL, Smith S, Ryan J: The role of hyperandrogenemia in the pathogenesis of ovarian hyperandrogenism. Fertil Steril 50:197-210, 1988

11. Dunaif A, Segal KR, Futterweit W, et al: Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 38:1165-1174, 1989

12. Lanzone A, Villa P, Fulghesu AM, et al: The growth hormone response to growth hormone–releasing hormone is blunted in polycystic ovary syndrome: Relationship with obesity and hyperinsulinemia. Hum Reprod 10:1653-1657, 1995

13. Lee EJ, Park KH, Lee BS, et al: Growth hormone response to L-dopa and pyridostigmine in women with polycystic ovarian syndrome. Fertil Steril 660:53-57, 1993

14. Bruni J, Watkins W, Yen SSC: B-endorphin in the human pancreas. J Clin Endocrinol Metab 49:649-651, 1979

15. Givens JR, Wiedeman E, Andersen RM, et al: Beta-endorphin

and β-lipotrophin plasma levels in hirsute women: Correlation with body weight. J Clin Endocrinol Metab 50:975-976, 1980

16. Fulghesu AM, Lanzone A, Cucinelli F, et al: Long term naltrexone treatment reduces the exaggerated insulin secretion in patients with polycystic ovary disease. Obstet Gynecol 82:191-196, 1993

17. New MI, Lorenzen F, Lerner AJ, et al: Genotyping steroid 21-hydroxylase deficiency: Hormonal reference data. J Clin Endocrinol Metab 57:320-326, 1983

18. Bray GA: Classification and evaluation of the obesities. Med Clin North Am 73:161-184, 1989

19. Blum WF, Ranke MB, Kietzmann K, et al: A specific radioimmunoassay for the growth hormone (GH)-dependent somatomedin binding protein: Its use for diagnosis of GH deficiency. J Clin Endocrinol Metab 70:1292-1298, 1990

20. Juul A, Main K, Blum WF, et al: The ratio between serum insulin-like growth factor (IGF)-1 and the IGF binding proteins (IGFBP-1, -2, -3) decreases with age and is decreased in acromegalic patients. Clin Endocrinol (Oxf) 41:85-93, 1994

21. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039-1057, 1979

22. Pasquali R, Casimirri F, Venturoli S, et al: Body fat distribution has weight-independent effects on clinical hormonal and metabolic features of women with polycystic ovary syndrome. Metabolism 43:706-713, 1994

23. Barbieri RL, Ryan KJ: Hyperandrogenism, insulin resistance and acanthosis nigricans syndrome: A common endocrinopathy with distinct pathophysiology features. Am J Obstet Gynecol 147:90-101, 1983

24. Lanzone A, Fulghesu AM, Andreani CL, et al: Insulin secretion in polycystic ovarian disease: Effect of ovarian suppression by GnRH agonist. Hum Reprod 5:143-149, 1990

25. Sternbach HA, Annitto W, Pottash ALC, et al: Anorectic effects of naltrexone in man. Lancet 1:388-389, 1982

26. Fulghesu AM, Ciampelli M, Fortini A, et al: Effect of opioid blockade on insulin metabolism in polycystic ovarian disease. Hum Reprod 10:2253-2257, 1995

27. Vettor R, Macor C, Rossi E, et al: Effect of naltrexone treatment on insulin secretion, insulin action and postprandial thermogenesis in obesity. Horm Metab Res 26:188-194, 1994

28. Ghigo E, Procopio M, Boffano GM, et al: Arginine potentiates but does not restore the blunted growth hormone response to growth hormone releasing hormone in obesity. Metabolism 41:560-563, 1992

29. Grossman A, Stubbs WA, Gailland RC, et al: Studies of the opiate control of prolactin, GH, and TSH. Clin Endocrinol (Oxf) 14:381-386, 1981

30. Janik J, Klosterman S, Parman R, et al: Multiple opiate receptor sub-types are involved in the stimulation of growth hormone release by β-endorphin in female rats. Neuroendocrinology 70:69-75, 1990

31. Barbarino A, De Marinis L, Mancini A, et al: Sex-related naloxone influence on growth hormone releasing hormone–induced growth hormone secretion in normal subjects. Metabolism 36:105-109, 1987

32. Isaacs RE, Gardner DG, Baxter JD: Insulin regulation of rat growth hormone gene expression. Endocrinology 120:2022-2028, 1987

33. Dozio N, Scavini M, Beretta A, et al: In vivo metabolic effects of insulin-like growth factor-I not mediated through the insulin receptor. J Clin Endocrinol Metab 80:1325-1328, 1995

34. Cordido F, Casanueva FF, Vidal JI, et al: Study of insulin-like growth factor 1 in human obesity. Horm Res 36:187-191, 1991

35. Rasmussen MH, Hvidberg A, Juul A, et al: Massive weight loss restores 24-hour growth hormone release profiles and serum insulin-like growth factor 1 levels in obese subjects. J Clin Endocrinol Metab 80:1407-1415, 1995

36. Rasmussen MH, Frystyk J, Andersen T, et al: The impact of obesity, fat distribution, and energy restriction on insulin-like growth factor-I (IGF-1), IGF-binding protein-3, insulin, and growth hormone. Metabolism 43:315-319, 1994

37. Rinderknecht E, Humbel RE: The amino acid sequence of human insulin-like growth factor-I and its structural homology with proinsulin. J Biol Chem 253:2769-2776, 1978

38. Morris RS, Carmina E, Vijod MA, et al: Alterations in the sensitivity of serum insulin-like growth factor 1 and insulin-like growth factor binding protein-3 to octreotide in polycystic ovary syndrome. Fertil Steril 63:742-746, 1995